PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Fatty liver index, albuminuria and the association with chronic kidney disease: a population-based study in China
AUTHORS	Sun, Kan; Lin, Diaozhu; Li, Feng; Qi, Yiqin; Feng, Wanting; Yan, Li; Chen, Chaogang; Ren, Meng; Liu, Dan

VERSION 1 – REVIEW

REVIEWER	Carlo Bruno Giorda Diabetes and Metabolism Unit ASL Torino 5 via De Maria 1 !0023 Chieri ITALY
REVIEW RETURNED	29-Aug-2017

GENERAL COMMENTS	This is an interesting paper in that it confirms, in a cross-sectional way, the already known correlation/association between liver steatosis and klidney damage. It can not be considered original as there are several papers on this topic in the literature. However two original aspects are reported: 1. The use of albuminuria as a measure of kidney damage 2. The findings in a Chinese (Asiatic) population which are likely to be different from previous analysis carried out in caucasic subjects Major points Beyond the linear and quartile analysis, I suggest performing an additional analysis using the appropriate cut- off for NAFLD in the chinese population (it is known that in caucasian subjects it is 60). It would be informative to know whether (and how) established NAFLD is associated with kidney damage. It is not correct that the population is the largest ever surveyed. Similar analysis, including longitudinal observation, have been published in larger populations. (See Giorda C et al. Occurrence over time and regression of nonalcoholic fatty liver disease in type 2 diabetes. Diabetes Metab Res Rev. 2017 May;33(4)). I advice the authors to make comparisons with those data in the discussion section.

REVIEWER	DR OYEKOYA AYONRINDE FIONA STANLEY HOSPITAL AUSTRALIA
REVIEW RETURNED	18-Oct-2017

GENERAL COMMENTS	The authors have examined associations between fatty liver index (FLI) as a surrogate for hepatic steatosis, and chronic kidney disease defined by reduced eGFR or albuminuria, in a large community-based population of middle-aged and elderly adults in China. The manuscript addresses an important subject of 2 common conditions with some shared risk factors. It is mostly well-written though some English language editing is required, particularly in the earlier part of the paper. I have a few comments/ queries: 1. Despite the authors acknowledging the absence of a FLI threshold defining steatosis in their population, population estimates of NAFLD based on previous Chinese population studies or from previous studies comparing FLI with other methods of diagnosis steatosis would be useful. 2. Also, a reference to the local population prevalence of obesity and for the BMI threshold used to define obesity. 3. An important omission is a comment regarding the local epidemiology of HBV and HCV, which are both prevalent in China and can be associated with liver disease and kidney disease. Were they checked in the cohort. This is a potential limitation. 4. Creatinine results should be included in Table 1. 5. The study cited in reference 2 is a survey conducted between 2007 and 2010, though published in 2012. 6. It is a pity that alcohol intake was not quantified, as this influences the FLI and doesn't permit comparisons between and within alcoholic and nonalcoholic fatty liver disease groups. 7. The term fatty degeneration of the liver is an old fashioned term, no longer in general use. 8. There is conflicting data regarding amounts of alcohol consumed and both insulin sensitivity and albuminuria that may be worth incorporating in the discussion. 9. Abbreviations SBP and DBP need to be expanded to systolic blood pressure and diastolic blood pressure somewhere in the text, though shown in Table 1. 10. Since BMI, WC, GGT, TG are components of FLI, is it practical to have adjusted for these in Table 3 model 3? 11. Please present the p values for other inter-group comparisons in Table 1 12. The outcome measures are detailed in the abstract but not in the manuscript text.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Carlo Bruno Giorda
Institution and Country: Diabetes and Metabolism Unit, ASL Torino 5, via De Maria 1, 0023 Chieri ITALY
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This is an interesting paper in that it confirms, in a cross-sectional way, the already known correlation/association between liver steatosis and klidney damage. It can not be considered original as there are several papers on this topic in the literature. However two original aspects are reported:

1. The use of albuminuria as a measure of kidney damage
2. The findings in a Chinese (Asiatic) population which are likely to be different from previous analysis carried out in caucasic subjects

Major points

Beyond the linear and quartile analysis, I suggest performing an additional analysis using the appropriate cut-off for NAFLD in the chinese population (it is known that in caucasian subjects it is 60). It would be informative to know whether (and how) established NAFLD is associated with kidney damage.

Response: Thank you for your revision and we appreciate very much for your comments. The manuscript has certainly benefited from all these insightful suggestions.
Originally, FLI＞60 was suggested to rule in fatty liver disease in Caucasian subjects. However, the optimal cutoff value of FLI for predicting fatty liver disease was different in Asian populations. Based on recent research, the FLI could accurately identify NAFLD and the optimal cut-off point was 30 in middle-aged and elderly Chinese [1]. Therefore, we classified the study population in non-current drinking group into two groups as follows: NAFLD group (FLI ≥ 30) and non-NAFLD group (FLI < 30). The prevalence of increased urinary albumin excretion was 51.6% and 29.6% in FLI established NAFLD and non-NAFLD group (P < 0.0001). Similar trends were detected in the prevalence of CKD (NAFLD group: 49.9%; non-NAFLD group: 31.5%, P < 0.0001). Compared with participants in the non-NAFLD group, those in NAFLD group had higher prevalence of increased urinary albumin excretion (OR 1.58, 95 % CI 1.18 - 2.13) and CKD (OR 1.39, 95 % CI 1.05 - 1.82) in multivariate logistic regression analyses. Related "Method and Result" was modified in the revised manuscript. ("Method" section, L205-208; "Result" section, L278 -284).

[1]. Huang X, Xu M, Chen Y, et al. Validation of the Fatty Liver Index for Nonalcoholic Fatty Liver Disease in Middle-Aged and Elderly Chinese. Medicine 2015;94(40):e1682.

Comment: It is not correct that the population is the largest ever surveyed. Similar analysis, including longitudinal observation, have been published in larger populations. (See Giorda C et al. Occurrence over time and regression of nonalcoholic fatty liver disease in type 2 diabetes. Diabetes Metab Res Rev. 2017 May;33(4)). I advise the authors to make comparisons with those data in the discussion section.

Response: We appreciate very much for your comments and reminding. Actually, as the time of publication of the literature “Giorda C et al. Occurrence over time and regression of nonalcoholic fatty liver disease in type 2 diabetes. Diabetes Metab Res Rev. 2017 May;33(4)”, we are sorry for the description by saying that the population is the largest ever surveyed. Because the value of FLI for evaluating lipid metabolism was quite different in Asian populations when compared with Caucasian subjects. Therefore, in the revised manuscript, we described the present study as the largest population-based study to explore the association of FLI with both albuminuria and CKD in Asian population.

Following your suggestion, we also discussed the interesting publication by Giorda C et al. in the revised manuscript and related information was presented as: “Recently, an interesting study by Giorda C et al. [1] reported that NAFLD is a dynamic condition in type 2 diabetes subjects and about 5% Italian diabetic patients entering or leaving FLI assessed NAFLD status every year. They found that male sex and established organ damage, especially kidney function, were independent risk predictors for the dynamic NAFLD condition in a longitudinal 3-year analysis. As the similarity in traditional risk factors for both NAFLD and CKD, relationship between the prevalence of earlier stages of kidney damage and the incidence of NAFLD is complex. Longitudinal observation of our cohort are needed to be carried out to determine whether such dynamic condition existed in the Chinese, especially in those with type 2 diabetes.” (“Discussion” section, L355 -364).

In the end, thank you again for having given us the opportunity to revise the manuscript. The manuscript has certainly benefited from these insightful revision suggestions. We carefully addressed the comments point-by-point and changed our manuscript accordingly. Nevertheless, we are prepared to revise our manuscript further, should it be necessary.

[1]. Giorda C, Forlani G, Manti R, et al. Occurrence over time and regression of nonalcoholic fatty liver disease in type 2 diabetes. Diabetes/metabolism research and reviews 2017;33(4).

Reviewer: 2
Reviewer Name: DR OYEKOYA AYONRINDE
Institution and Country: FIONA STANLEY HOSPITAL, AUSTRALIA
Please state any competing interests or state ‘None declared’: NONE DECLARED

Please leave your comments for the authors below
The authors have examined associations between fatty liver index (FLI) as a surrogate for hepatic steatosis, and chronic kidney disease defined by reduced eGFR or albuminuria, in a large community-based population of middle-aged and elderly adults in China. The manuscript addresses an important subject of 2 common conditions with some shared risk factors. It is mostly well-written though some English language editing is required, particularly in the earlier part of the paper. I have a few comments/ queries:

1. Despite the authors acknowledging the absence of a FLI threshold defining steatosis in their population, population estimates of NAFLD based on previous Chinese population studies or from previous studies comparing FLI with other methods of diagnosis steatosis would be useful.

Response: Thank you for your revision and we appreciate very much for your comments. The manuscript has certainly benefited from all these insightful suggestions.

Following your suggestion, we discussed the study that estimates of NAFLD based on previous Chinese population in the revised manuscript. “As a surrogate marker of histological fatty liver, FLI is defined as the accumulation of excessive liver fat. Based on the former researches, FLI has been proven accurate in detecting fatty liver against liver ultrasound and demonstrating the presence of hepatic fat against magnetic resonance spectroscopy [1-4].”
“Originally, FLI＞60 was suggested to rule in NAFLD in Caucasian subjects. However, the optimal cutoff value of FLI for predicting NAFLD was different in Asian populations. Based on recent research, the FLI could accurately identify NAFLD and the optimal cut-off point was 30 in middle-aged and elderly Chinese [1].”
We also performing an additional analysis using the cut-off for NAFLD to analyses how established NAFLD is associated with kidney damage. We classified the study population in non-current drinking group into two groups as follows: NAFLD group (FLI ≥ 30) and non-NAFLD group (FLI < 30). The prevalence of increased urinary albumin excretion was 51.6% and 29.6% in FLI established NAFLD and non-NAFLD group (P < 0.0001). Similar trends were detected in the prevalence of CKD (NAFLD group: 49.9%; non-NAFLD group: 31.5%, P < 0.0001). Compared with participants in the non-NAFLD group, those in NAFLD group had higher prevalence of increased urinary albumin excretion (OR 1.58, 95 % CI 1.18 - 2.13) and CKD (OR 1.39, 95 % CI 1.05 - 1.82) in multivariate logistic regression analyses.
Related “Method and Result” was modified in the revised manuscript. (“Method” section, L205-208; “Result” section, L278-284; “Discussion” section, L313-317).

[1]. Huang X, Xu M, Chen Y, et al. Validation of the Fatty Liver Index for Nonalcoholic Fatty Liver Disease in Middle-Aged and Elderly Chinese. Medicine 2015;94(40):e1682.
[2]. Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC gastroenterology 2006;6:33.
[3]. Gastaldelli A, Kozakova M, Hojlund K, et al. Fatty liver is associated with insulin resistance, risk of coronary heart disease, and early atherosclerosis in a large European population. Hepatology 2009;49(5):1537-44.
[4]. Kozakova M, Palombo C, Eng MP, et al. Fatty liver index, gamma-glutamyltransferase, and early carotid plaques. Hepatology 2012;55(5):1406-15.

2. Also, a reference to the local population prevalence of obesity and for the BMI threshold used to define obesity.

Response: We appreciate very much for your comments. Following your suggestion, we changed and cited the relevant references in the revised manuscript after a comprehensive literature search. Related “Methods and Discussion” was modified in the revised manuscript.
“BMI was calculated as weight in kilograms divided by height in meters squared (kg/m2). Obesity was defined as BMI equal or greater than 28 and overweight was defined as BMI equal or greater than 24 and less than 28 [1].” “Methods” section, L171 -173”
“Prevalence of obesity was 7.9% (8.4% in males and 7.6% in females) in southern China, which has increased dramatically over the past several decades [2].” “Discussion” section, L305 -306”

[1]. Xi B, Liang Y, He T, et al. Secular trends in the prevalence of general and abdominal obesity among Chinese adults, 1993-2009. Obesity reviews: an official journal of the International Association for the Study of Obesity 2012;13(3):287-96.
[2]. Hu L, Huang X, You C, et al. Prevalence of overweight, obesity, abdominal obesity and obesity-related risk factors in southern China. PloS one 2017;12(9):e0183934.

3. An important omission is a comment regarding the local epidemiology of HBV and HCV, which are both prevalent in China and can be associated with liver disease and kidney disease. Were they checked in the cohort? This is a potential limitation.

Response: We appreciate very much for your comments. Viral hepatitis infection is prevalent in China and can be associated with liver disease and kidney disease. We do agree with you that lack of the local epidemiologic data of HBV and HCV is a potential limitation of the present study.

Following your suggestion, we discussed such limitation in the revised manuscript: “Viral hepatitis infection is one of the most serious infectious diseases worldwide, which can be associated with both liver and kidney disease. Recent survey data showed that the hepatitis B surface antigen and anti-hepatitis C virus–positive rates were already 6.1% and 3.0% in China [1]. Epidemiology of viral hepatitis infection by hepatitis B virus (HBV) and hepatitis C virus (HCV) serological testing, therefore, should be also be evaluate to strength the findings of the present study.” “Discussion” section, L395-401”

[1]. Zhang Q, Qi W, Wang X, et al. Epidemiology of Hepatitis B and Hepatitis C Infections and Benefits of Programs for Hepatitis Prevention in Northeastern China: A Cross-Sectional Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2016;62(3):305-12.

4. Creatinine results should be included in Table 1.

Response: Such information was missing in the original manuscript. Thank you very much for your reminding. Related information of creatinine results was presented in the revised manuscript in Table 1.

Table 1. Characteristics of study population by FLI quartiles

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
n (%)	2360 (25.01)	2359 (24.99)	2359 (24.99)	2360 (25.01)	
Fatty liver index	5.00 (3.27 – 6.74)	13.23 (10.76 – 15.99)	26.96 (22.74 – 31.75)	54.71 (45.40 – 68.10)	
Serum creatinine (μmol/L)	65.3 ± 15.5	68.8 ± 16.0	70.5 ± 16.0	74.9 ± 17.2	< 0.0001

5. The study cited in reference 2 is a survey conducted between 2007 and 2010, though published in 2012.

Response: Thank you very much for the revision. Related study was cited and modified in the revised manuscript as “Recent national survey conducted between 2007 and 2010 reported that the prevalence of CKD was 10.8%, representing an estimated 119.5 million patients in China with chronic kidney damage [1].” “Introduction” section, L108 -110”

[1]. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet 2012;379(9818):815-22.

6. It is a pity that alcohol intake was not quantified, as this influences the FLI and doesn't permit comparisons between and within alcoholic and nonalcoholic fatty liver disease groups.

Response: We appreciate very much for your comments.
Following your suggestion, we further discussed such limitation in the revised manuscript: “A significant association of FLI with increased urinary albumin excretion and CKD only detected in subjects without current alcohol consumption. Average daily alcohol intake influences the FLI and missing such data in the present study doesn't permit comparisons between and within alcoholic and nonalcoholic fatty liver disease groups. To better discriminate alcoholic fatty liver disease and non-alcoholic fatty liver disease, further studies need to clearly described the precise exposure of alcohol use by collecting histories of alcohol intake in a quantitative manner.” “Discussion” section, L388 -395”

7. The term fatty degeneration of the liver is an old fashioned term, no longer in general use.

Response: We agree with your suggestion and “fatty degeneration of the liver” was changed to “steatosis in hepatic tissue” in the revised manuscript. Related section was modified in the revised manuscript as “The noninvasive technique is not sensitive enough to detect mild steatosis and does not allow precise quantification of severity of steatosis in hepatic tissue.” and “The superiority of this non-invasive assessment techniques is that a higher score will indicate a higher degree of steatosis in hepatic tissue.” “Discussion” section, L311 -313 & L317 -318”

8. There is conflicting data regarding amounts of alcohol consumed and both insulin sensitivity and albuminuria that may be worth incorporating in the discussion.

Response: We appreciate very much for your comments.
Following your suggestion, we discussed recent conflicting data regarding amounts of alcohol consumed with both insulin sensitivity and albuminuria. Related section was modified in the revised manuscript as “Alcohol consumption can profoundly disturb the lipid metabolism which have prominent effects on the hepatic tissue steatosis and insulin sensitivity [1]. However, potential health effects regarding alcohol consumption in this field is also worth attaching attention. A meta-analysis of intervention studies by Schrieks et al [2]. showed that moderate alcohol intake could improve insulin sensitivity by decreasing fasting insulin level in women. Recently, a prospective cohort study found that alcohol consumption was consistently inversely associated with urinary albumin excretion and the risk of developing CKD [3]. Therefore, advice concerning alcohol consumption to subjects with low-grade hepatic tissue steatosis should consider the full range of benefits and risks, especially among those who drink moderately.” “Discussion” section, L365 -374”

[1]. Parker R, Kim SJ, Gao B. Alcohol, adipose tissue and liver disease: mechanistic links and clinical considerations. Nature reviews Gastroenterology & hepatology 2017.
[2]. Schrieks IC, Heil AL, Hendriks HF, et al. The effect of alcohol consumption on insulin sensitivity and glycemic status: a systematic review and meta-analysis of intervention studies. Diabetes care 2015;38(4):723-32.
[3]. Koning SH, Gansevoort RT, Mukamal KJ, et al. Alcohol consumption is inversely associated with the risk of developing chronic kidney disease. Kidney international 2015;87(5):1009-16.

9. Abbreviations SBP and DBP need to be expanded to systolic blood pressure and diastolic blood pressure somewhere in the text, though shown in Table 1.

Response: We appreciate very much for your comments and reminding. Related information was presented in the revised manuscript as “Model 3 is adjusted for age, sex, BMI, WC, current smoking status, current drinking status, physical activity, systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, LDL-C, fasting insulin, ALT, AST and γ-GGT. Odds ratios (OR) and the corresponding 95% confidence intervals (95% CI) were calculated.” “Method” section, L233 -237”

10. Since BMI, WC, GGT, TG are components of FLI, is it practical to have adjusted for these in Table 3 model 3?

Response: We appreciate the comments. To be comparable with other studies and to direct clinical work for weight and lipids control, we prefer to show FLI as an indicator, not just a calculating index, to reflect the real condition of kidney disease in Chinese. Similar analysis for FLI could be found in previous study [1]. However, adjusted these variables simultaneously may suffer from collinear problems, which could also influence numerical estimates and result interpreting.
Therefore, following your suggestion, we included a new Model-3 that with components of FLI un-adjusted in the revised manuscript (see following Table-3). As shown in Table 3, compared with participants in quartile 1 of FLI, logistic regression analysis showed that participants in quartile 4 have a significant correlation with increased odds of increased urinary albumin excretion and CKD in each model.

[1]. Jager S, Jacobs S, Kroger J, et al. Association between the Fatty Liver Index and Risk of Type 2 Diabetes in the EPIC-Potsdam Study. PloS one 2015;10(4):e0124749.

Table 3. The risk of prevalent albuminuria and CKD according to quartiles of FLI

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Increased urinary albumin excretion	Model 1	1	1.34 (1.01 – 1.79)	1.76 (1.34 – 2.31)	3.46 (2.70 – 4.44)	< 0.0001
	Model 2	1	1.29 (0.97 – 1.72)	1.66 (1.27 – 2.19)	3.25 (2.53 – 4.17)	< 0.0001
	Model 3	1	0.94 (0.66 – 1.33)	1.13 (0.81 – 1.59)	2.22 (1.60 – 3.07)	< 0.0001
	Model 4	1	0.96 (0.66 – 1.39)	1.17 (0.77 – 1.77)	2.30 (1.36 – 3.90)	0.001
CKD	Model 1	1	1.47 (1.13 – 1.90)	1.79 (1.39 – 2.30)	3.49 (2.77 – 4.39)	< 0.0001
	Model 2	1	1.39 (1.07 – 1.80)	1.65 (1.28 – 2.12)	3.16 (2.51 – 3.99)	< 0.0001
	Model 3	1	0.99 (0.73 – 1.36)	1.03 (0.75 – 1.40)	1.95 (1.44 – 2.64)	< 0.0001
	Model 4	1	1.00 (0.71 – 1.40)	1.03 (0.70 – 1.51)	1.93 (1.18 – 3.15)	0.012

Data are odds ratios (95% confidence interval). Participants without increased urinary albumin excretion or CKD are defined as 0 and with increased urinary albumin excretion or CKD as 1.
Model 1 is unadjusted.
Model 2 is adjusted for age.
Model 3 is adjusted for age, sex, current smoking status, current drinking status, physical activity, SBP, DBP, LDL-C, fasting insulin, ALT and AST.
Model 4 is adjusted for age, sex, BMI, WC, current smoking status, current drinking status, physical activity, SBP, DBP, TG, LDL-C, fasting insulin, ALT,

11. Please present the p values for other inter-group comparisons in Table 1

Response: We appreciate the comments. Following your suggestion, related “Table-1” was presented the p values for other inter-group comparisons in the revised manuscript. *: $P < 0.05$ compared with Quartile 1 of fatty liver index; #: $P < 0.05$ compared with Quartile 2 of fatty liver index; &: $P < 0.05$ compared with Quartile 3 of fatty liver index.

Table 1. Characteristics of study population by FLI quartiles

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
n (%)	2360 (25.01)	2359 (24.99)	2359 (24.99)	2360 (25.01)	
Fatty liver index	5.00 (3.27 – 6.74)	13.23 (10.76 – 15.99)	26.96 (22.74 – 31.75)	54.71 (45.40 – 68.10)	
Urinary albumin to creatinine ratio (mg/g)	7.65 (5.59 – 11.12)	8.01 (5.64 – 11.71)	8.06 (5.73 – 11.83)*	8.93 (5.96 – 15.01)*#&	< 0.0001
Age (years)	54.3 ± 7.8	55.8 ± 7.9*	56.5 ± 7.9*#	56.9 ± 8.3*#	< 0.0001
Male [n (%)]	427 (18.09)	593 (25.17)	701 (29.72)	975 (41.31)	< 0.0001
BMI (kg/m^2)	20.6 ± 2.0	22.9 ± 2.0*&	24.4 ± 2.1*#	26.8 ± 3.5*#&	< 0.0001
WC (cm)	72.0 ± 5.8	79.3 ± 5.4*&	84.1 ± 5.5*#	91.3 ± 8.5*#&	< 0.0001
…	…	…	…	….	…
HDL-C (mmol/L)	1.45 ± 0.41	1.37 ± 0.35*&	1.29 ± 0.31*#	1.19 ± 0.28*#&	< 0.0001
LDL-C (mmol/L)	2.82 ± 0.90	3.19 ± 0.94*&	3.31 ± 0.91*#	3.28 ± 0.95*#	< 0.0001
FPG (mmol/L)	5.23 (4.89 – 5.61)	5.33 (4.95 – 5.80) *&	5.47 (5.05 – 5.96) *#	5.73 (5.23 – 6.42) *#&	< 0.0001
Fasting insulin (μIU/ml)	5.10 (3.90 – 6.50)	6.50 (5.00 – 8.40) *&	7.90 (6.10 – 10.30) *#	10.50 (7.80 – 13.70) *#&	< 0.0001
ALT (U/L)	10.0 (8.0 – 14.0)	12.0 (9.0 – 16.0) *&	13.0 (10.0 – 17.0) *#	17.0 (12.0 – 24.0) *#&	< 0.0001
AST (U/L)	17.0 (14.0 – 20.0)	18.0 (15.0 – 21.0) *&	18.0 (15.0 – 22.0) *#	20.0 (17.0 – 25.0) *#&	< 0.0001

1. Data were means ± SD or medians (interquartile ranges) for skewed variables or numbers (proportions) for categorical variables.
2. P for trend was calculated for the linear regression analysis tests across the groups. P values were for the ANOVA or χ^2 analyses across the groups.
3. *P < 0.05 compared with Quartile 1 of fatty liver index; #P < 0.05 compared with Quartile 2 of fatty liver index; &P < 0.05 compared with Quartile 3 of fatty liver index.
4. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GGT, γ-glutamyltransferase; eGFR, estimated glomerular filtration rate.

12. The outcome measures are detailed in the abstract but not in the manuscript text.

Response: We appreciate very much for your comments and reminding. Related outcome measures are detailed and presented in the revised manuscript as “The primary and secondary outcome measures were increased urinary albumin excretion and chronic kidney disease (CKD), respectively. Increased urinary albumin excretion was defined according to the ACR ranges greater or equal than 30 mg/g. Chronic kidney disease (CKD) was defined as eGFR less than 60 mL/min per 1.73 m² or presence of albuminuria (ACR greater or equal than 30 mg/g).” “Method” section, L201-205”
In the end, thank you again for having given us the opportunity to revise the manuscript. We carefully addressed the comments point-by-point and changed our manuscript accordingly. Nevertheless, we are prepared to revise our manuscript further, should it be necessary.

VERSION 2 – REVIEW

REVIEWER	Carlo Bruno Giorda Diabetes Endocrine Uniti ASL TO 5 via De Maria 1 10023 Chieri Italy
REVIEW RETURNED	26-Nov-2017

GENERAL COMMENTS	The authors answered my questions correctly.

REVIEWER	FIONA STANLEY HOSPITAL AUSTRALIA
REVIEW RETURNED	28-Nov-2017

GENERAL COMMENTS	The authors have largely responded to my comments and queries and this is a significant improvement on the earlier version of this manuscript. I have a few comments: I had hoped that a population-based prevalence of NAFLD using a defined modality would be included in the introduction or discussion for comparison of the results from this study with other similar populations using FLI, ultrasound, MRI etc. Further English language editing is required. As a limitation it should be expressed that the calculated FLI may relate to various liver diseases with associated steatosis and not only NAFLD, despite the fact that metabolic disturbances make obesity related steatosis likely. A concluding comment on why CKD or albuminuria is relevant to chronic liver disease or steatosis is worth considering i.e. the implications of the findings.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Carlo Bruno Giorda
Institution and Country: Diabetes Endocrine Uniti, ASL TO 5, via De Maria 1 10023 Chieri, Italy
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Comment: The authors answered my questions correctly.

Reviewer: 2
Reviewer Name: OYEKOYA AYONRINDE
Institution and Country: FIONA STANLEY HOSPITAL, AUSTRALIA
Please state any competing interests or state 'None declared': NONE DECLARED

Please leave your comments for the authors below

Comment: The authors have largely responded to my comments and queries and this is a significant improvement on the earlier version of this manuscript.

Response: Thank you for your revision and we appreciate very much for your comments. The manuscript has certainly benefited from all these insightful suggestions.

I have a few comments: I had hoped that a population-based prevalence of NAFLD using a defined modality would be included in the introduction or discussion for comparison of the results from this study with other similar populations using FLI, ultrasound, MRI etc.

Response: We appreciate the comments of the editor. Following your suggestion, a population-based pooled prevalence of NAFLD using imaging as a diagnosis technique was included in the revised manuscript. Related "Discussion" was presented in the revised manuscript as "The problem of obesity and NAFLD are now increasingly recognized in the Asian population. Prevalence of obesity was 7.9%

(8.4% in males and 7.6% in females) in southern China, which has increased dramatically over the past several decades [1]. There is a strong correlation between established obesity and incidence of NAFLD. Pooled prevalence of NAFLD diagnosed by ultrasound, computed tomography scan and magnetic resonance was estimated to be 27.4% in subjects aged over 30 years from Asian countries [2]. Even among the non-obese Chinese, 8.9% developed NAFLD in five years from 2006 to 2011 [3]. Therefore, early and accurate diagnosis of NAFLD is of great importance." ("Discussion" section, L303 -311).

[1]. Hu L, Huang X, You C, et al: Prevalence of overweight, obesity, abdominal obesity and obesity-related risk factors in southern China. PLoS One 12:e0183934, 2017
[2]. Younossi ZM, Koenig AB, Abdelatif D, et al: Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 64:73-84, 2016
[3]. Xu C, Yu C, Ma H, et al: Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am J Gastroenterol 108:1299-304, 2013

Comment: Further English language editing is required.

Response: We appreciate very much for your comments and reminding. Following your suggestion, we have carefully checked our manuscript again and invited a native English speaker to recheck the revised manuscript - R2.

Comment: As a limitation it should be expressed that the calculated FLI may relate to various liver diseases with associated steatosis and not only NAFLD, despite the fact that metabolic disturbances make obesity related steatosis likely.

Response: We appreciate very much for your comments. Following your suggestion, we discussed such limitation in the revised manuscript: "… when evaluating the findings of the present study, the results should be interpreted cautiously due to possible bias from using the indirect indicator FLI to assess fatty liver disease. The calculated FLI may relate to various liver diseases with associated steatosis and not only NAFLD, despite the fact that metabolic disturbances make obesity related steatosis likely. The internal accuracy of FLI for evaluation hepatic steatosis should also be validated by using other techniques, before it can be employed for these purposes." "Discussion" section, L387-394"

Comment: A concluding comment on why CKD or albuminuria is relevant to chronic liver disease or steatosis is worth considering i.e. the implications of the findings.

Response: We appreciate very much for your comments and reminding. The concluding comment of the study was modified and presented in the Discussion section of the revised manuscript as "In conclusion, by including a large population based cohort, the present study provides evidence that increased FLI is independently associated with prevalence of albuminuria and CKD. Findings of the present study suggested us should pay more attention to albuminuria and eGFR variation in patients with dyslipidemia and fatty liver disease. Further prospective studies are necessary to verify our findings in external populations." "Discussion" section, L413-418"

In the end, thank you again for having given us the opportunity to revise the manuscript. We carefully addressed the comments point-by-point and changed our manuscript accordingly. Nevertheless, we are prepared to revise our manuscript further, should it be necessary.